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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/644,600	08/20/2003	Hans-Jurgen Gutke	60636(50551)	5568
21874	7590	01/25/2006	EXAMINER	
EDWARDS & ANGELL, LLP			MCINTOSH III, TRAVISS C	
P.O. BOX 55874			ART UNIT	
BOSTON, MA 02205			PAPER NUMBER	

1623

DATE MAILED: 01/25/2006

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary

Application No.

10/644,600

Applicant(s)

GUTKE ET AL.

Examiner

Traviss C. McIntosh

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-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

- 1) ☒ Responsive to communication(s) filed on 21 September 2005.
- 2a) ☐ This action is FINAL. 2b) ☒ This action is non-final.
- 3) ☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

- 4) ☒ Claim(s) 1 and 3-30 is/are pending in the application.
- 4a) Of the above claim(s) 11,12 and 14-30 is/are withdrawn from consideration.
- 5) ☐ Claim(s) _____ is/are allowed.
- 6) ☒ Claim(s) 1,3-10 and 13 is/are rejected.
- 7) ☐ Claim(s) _____ is/are objected to.
- 8) ☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

- 9) ☐ The specification is objected to by the Examiner.
- 10) ☐ The drawing(s) filed on _____ is/are: a) ☐ accepted or b) ☐ objected to by the Examiner.
Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).
Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).
- 11) ☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

- 12) ☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).
- a) ☐ All b) ☐ Some * c) ☐ None of:
1. ☐ Certified copies of the priority documents have been received.
 2. ☐ Certified copies of the priority documents have been received in Application No. _____.
 3. ☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

- | | |
|--|---|
| 1) <input checked="" type="checkbox"/> Notice of References Cited (PTO-892) | 4) <input type="checkbox"/> Interview Summary (PTO-413)
Paper No(s)/Mail Date. _____ |
| 2) <input type="checkbox"/> Notice of Draftsperson's Patent Drawing Review (PTO-948) | 5) <input type="checkbox"/> Notice of Informal Patent Application (PTO-152) |
| 3) <input type="checkbox"/> Information Disclosure Statement(s) (PTO-1449 or PTO/SB/08)
Paper No(s)/Mail Date _____ | 6) <input type="checkbox"/> Other: _____ |

DETAILED ACTION

The Amendment filed September 21, 2005 has been received, entered into the record, and carefully considered. The following information provided in the amendment affects the instant application by:

Claims 1, 5, 7-8, and 10 have been amended.

Claim 2 has been canceled.

Remarks drawn to rejections of Office Action mailed 11/12/2004 include:

Election/restriction: applicants are correct in stating that claims 1-12 and 14-30 are withdrawn.

Double Patenting rejection: which has been withdrawn due to applicant's amendments.

Applicants also indicated they would address the double patenting rejections when claims are indicated as allowable.

112 1st paragraph written description rejection: which has been withdrawn and a 112 1st paragraph enablement rejection has been set forth below.

112 2nd paragraph rejections: which have been overcome by applicant's amendments and have been withdrawn.

102(b) rejections: which have been overcome by applicant's amendments and have been withdrawn.

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An action on the merits of claims 1, 3-10, and 13 is contained herein below. The text of those sections of Title 35, US Code which are not included in this action can be found in a prior Office action.

Claim Rejections - 35 USC § 112

The following is a quotation of the first paragraph of 35 U.S.C. 112:

The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Claims 1, 3-10, and 13 are rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the enablement requirement. The claim(s) contains subject matter which was not described in the specification in such a way as to enable one skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention without undue experimentation. Applicants are not enabled for the combinations as instantly claimed.

Undue experimentation is a conclusion reached by weighing the noted factual considerations set forth below as seen in *In re Wands*, 858 F.2d 731, 737, 8 USPQ2d 1400, 1404 (Fed. Cir. 1988). A conclusion of lack of enablement means that, based on the evidence regarding a fair evaluation of an appropriate combination of the factors below, the specification, at the time the application was filed, would not have taught one skilled in the art how to make and/or use the full scope of the claimed invention without undue experimentation.

These factors include:

- (A) The breadth of the claims;
- (B) The nature of the invention;

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- (C) The state of the prior art;
- (D) The level of one of ordinary skill;
- (E) The level of predictability in the art;
- (F) The amount of direction provided by the inventor;
- (G) The existence of working examples; and
- (H) The quantity of experimentation needed to make or use the invention based on the content of the disclosure.

The breadth of the claims - The nature of the invention

Claim 1 is drawn to a compound defined as a transportophore which is coupled to 1-8 non-antibiotic agents via a bond or a linker having a molecular weight of up to 240 daltons wherein the transportophore is an amphiphilic molecule having a pKa value of 6.5 to 9.5 and having an immune selectivity ratio of at least 2. Claim 3 provides the transportophore is cyclic or heterocyclic, and claim 4 provides there is an attached sugar. Claim 5 limits the cyclic or heterocyclic compound to a macrolactone or macroether, and claim 6 provides there is a sugar in the macroether or macrolactone. Claim 7 provides the cyclic or heterocyclic structure is a macrolide or ketolide having an amino sugar, and claim 8 provides it has mono-, di-, or tri-basic groups. Claim 9 and 10 provide structural representations of the transportophore portion of the molecule (macrolides) and claim 13 provides various limitations to the linker.

It is noted that the list of the combination of compounds represented by the claims is likely in the tens of thousands, and quite possibly in the millions of possible compounds. The breadth of T, as being defined functionally (a transportophore), is extremely large, the breadth of L, also defined functionally (a linker), is extremely large, and the breadth of C, which is also defined functionally (a non-antibiotic therapeutic agent), is also extremely large. Taking these three large groups and combining them in any of the numerous combinations would encompass a tremendously large group of compounds.

The state of the prior art

Macrolides (which is the elected invention for T) are known to be used as antibiotics (see 6,046,171 for example) and to encompass many divergent functional groups (as seen by the instant claims and also the above patent). Non-antibiotic therapeutic agents are seen to encompass very divergent molecules being vectors, plasmids, organic molecules, peptides, proteins, tissue extracts, nucleic acids, genes, radiation, antibodies, and extracts, to name a few. It is noted that neither of these molecules are seen to have any common molecular structure, and any structure function relationship which may be present has not been divulged in the instant application. Combination therapy, and drug-drug interactions are known in the art to have various effects, and when physicians use several drugs in combination, they face the problem of knowing whether a specific combination in a given patient has the potential to result in an interaction, and if so, how to take advantage of the interaction if it leads to improvement in therapy or how to avoid the consequences on an interaction if they are adverse. A potential drug interaction refers to the possibility that one drug may alter the intensity of the pharmacological effects of another drug when given concurrently or in a conjugated form. The net result may be enhanced or diminished effects of one or both of the drugs, or the appearance of new effects which is not seen with either drug alone. The frequency of significant beneficial or adverse effects is unknown. The interaction between the drugs may be pharmacokinetic, i.e. alteration of the absorption, distribution, or elimination of one drug by another, or may be pharmacodynamic, i.e. interactions between agonists and antagonists at drug receptors. The most important drug-drug interactions occur with drugs that have serious toxicity and low therapeutic index, such that relatively small changes in drug level can have significant adverse consequences. Additionally,

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drug-drug interactions can be clinically important if the disease being controlled with the drug is serious or potentially fatal if left under treated. Drugs are known to interact at any point during their absorption, distribution, metabolism, or excretion; the result being an increase or decrease in concentration of the drug at that particular site of action. As individuals vary in their rates of disposition of an given drug, the magnitude of an interaction that alters pharmacokinetic parameters is not always predictable, but can be very significant. See Goodman & Gilman's: The Pharmacological Basis of Therapeutics, 10th Edition, McGraw-Hill Medical Publishing Division, 2001, pages 54-57.

The level of predictability in the art

As seen by Goodman & Gilman, the art of combination therapy is very unpredictable. Drug-drug interactions are known to be beneficial or adverse, yet there is no way to known until the drugs are actually tested in an individual.

The amount of direction provided by the inventor

The instant specification is not seen to provide adequate guidance which would allow the skilled artisan to extrapolate from the disclosure and examples provided to use the claimed method commensurate in the scope with the instant claims. There is a lack of data and examples which adequately represent the claims as written. Applicants have not provided any indication of what drugs might be toxic and what the drugs therapeutic indexes are. Applicants have merely listed various drugs in the specification.

The existence of working examples

The working examples set forth in the instant specification are drawn to methods of making various compounds claimed and tests using very few (5) compounds *in vitro*. The results

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showed that the 5 compounds tested produced very different ratios in the results, thus showing that the 5 compounds indeed react very differently. For example, the table on page 51 shows that compound 2 had a 2 fold concentration relative to the erythrocytes, and compound 10 had a 55 fold concentration relative to the erythrocytes, thus evidencing the fact that the results cannot be expected or predicted.

The quantity of experimentation needed to make and use the invention based on the content of the disclosure

Indeed, in view of the information set forth supra, the instant disclosure is not seen to be sufficient to enable one to use the conjugates of the transportophore linked to the non-antibiotic therapeutic agents, which encompasses thousands of possibly agents, without undue experimentation. It is noted that the specification should teach how to make and use the invention, not teach how to figure out for oneself how to make and use the invention. See *In re Gardner, 166 USPQ 138 (CCPA 1970)*. In order to practice the instant invention, one of ordinary skill in the art would be confronted with the undue burden to first determine if a drug actually performed any of the functionally described activities (i.e., test a compound to see if it is a transportophore having the claimed pKa value). If the skilled artisan did determine if the drug had the activity, then they would be required to determine whether the drug had any functional groups which would interact with the therapeutic agent, first *in vitro*, and then *in vivo*. And if the drug did interact, the artisan would be required to determine how they interacted, did the interaction provide adverse effects or beneficial effects, or produce completely new effects? They would be required to determine at what point in the patients system the effect occurred, and determine what is needed to ensure the patient was effectively treated. One of skill in the art

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would not be able to use the invention as instantly claimed without undue experimentation as the art recognizes the unpredictability of drug-drug interactions.


Conclusion

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Traviss C. McIntosh whose telephone number is 571-272-0657. The examiner can normally be reached on M-F 9:30-6:00.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Shaojia A. Jiang can be reached on 571-272-0627. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see <http://pair-direct.uspto.gov>. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free).

Traviss C. McIntosh III
January 20, 2006



James O. Wilson
Supervisory Patent Examiner
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